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10/524,724	10/18/2006	**Matthew Graeme Dunckley**	E072 1050.1	8410

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EXAMINER	
ZARA, JANE J	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/524,724	DUNCKLEY ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 April 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23,26,28,30-38,40-43 and 61-78* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23, 26, 28, 30-38, 40-43, 61-78* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4-20-09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communication filed 4-20-09.

Claims 23, 26, 28, 30-38, 40-43, 61-78 are pending in the instant application.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Maintained Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 23, 26, 28, 30-38, 40-43, 61-78 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for the reasons of record set forth in the Office action mailed 11-18-07, and as set forth below.

Claims 23, 26, 28, 30-38, 40-43, 61-78 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the in vitro increase in splicing efficiency by enhanced inclusion of exon 7 within SMN2 using particularly described 5'GGA and 5'GAA containing antisense oligonucleotides of SEQ ID NOs. 8 and 10, does not reasonably provide enablement for methods of recruiting RNA splicing

factors, enhancing exonic incorporation, and recruiting any splicing factor to any target RNA species for treating any condition characterized by defective RNA splicing in an individual, comprising the administration of a representative number of species of the broad genus of compounds claimed for the reasons of record set forth in the Office action mailed 11-18-07, and as set forth below.

Applicant's arguments filed 4-20-09 have been fully considered but they are not persuasive. Applicant argues that adequate written description has been provided because the entire sequence of the human genome has been available for many years, alone with the genome of other species, and a person of skill in the art would readily be able to provide the sequence of a large number of suitable nucleic acid molecules for targeting to a specific splice site on a target RNA sequence. Applicant also argues that the claimed invention is based on the surprising finding that a splicing enhancer sequence part of an oligonucleotide tail can enhance splicing in trans when attached to a pre-mRNA via base pairing of the annealing portion of the oligonucleoitde. Applicant also argues that numerous other splicing enhancer sequences are described in the instant application and lists a number of RNA motifs that are recognized by human SR proteins. In addition, Applicant sites several post-filing references that teach splicing enhancer sequences.

Applicant also argues that the instantly claimed invention is fully enabled, and that the Office has not provided any reasons to doubt that one skilled in the art would have been able to make and use the invention without undue experimentation. Applicant argues that the enablement rejection is inconsistent with the obviousness

rejection of record, and that the references cited in the enablement rejection do not accurately reflect the state of the art. Applicant cites several references that discuss clinical success with regard to other gene therapy endeavors in support of his arguments.

The claims are broadly drawn to methods of recruiting any RNA splicing factor to any target RNA species for treating any condition characterized by defective RNA splicing in an individual, comprising the administration of a nucleic acid molecule comprising a first domain which forms a specific binding pair with a target sequence which is within 100 nucleotides of any defective RNA splicing site on a target RNA, and which nucleic acid molecule further comprises a second specific binding pair with any RNA splicing factor and which second domain is optionally complementary or non-complementary to the second target RNA species.

Contrary to Applicant's assertions, the prior art and the instant disclosure, at the time of filing, do not provide adequate written description for broad genus of compounds claimed. The specification, claims and the art do not adequately describe the distinguishing features or attributes concisely shared by the members of the genus of compounds claimed, and which provide for the functions claimed, which functions include recruiting any splicing factor to any target RNA species for treating any condition characterized by defective RNA splicing in an individual.

The specification teaches the characterization of a series of oligonucleotides with tails for recruiting hTRA2β and SF2/ASF, whereby a specific increase in the proportion of exon 7 inclusion in SMN2 mRNA was observed in vitro when using 5'GAA but not

with 5'GGA. *See, e.g.,* page 65 of the instant disclosure, teaching that hTra2-B1 is thought to be rendered inaccessible to 5'GGA due to possible secondary structural constraints. See also page 66, showing that the addition of hTra2B to the nuclear extract stimulates inclusion in SMN1, but has relatively little effect on SMN2 in the presence of either 5'GGA or 5'GAA, suggesting that other factors limit improvements in corrective efficiency that appear unpredictable.

Contrary to Applicant's assertions, the references cited in support of the enablement rejection accurately the unpredictability in the art of gene therapy that remain today. The success of a particular oligonucleotide to provide in vivo affects does not necessarily provide assurance for clinical success for a different effector molecule (e.g. an inhibitory oligoncucleotide) to successfully target a different target gene or to exert its effects predictably in an organism. One situation is not extrapolatable to another situation, especially where different effector molecules are used to target different genes of interest, or are involved in different biochemical mechanisms.

The citations provided by Applicant help illustrate the unpredictability of the field of gene therapy, and help illustrate why adequate written description is lacking for the instant invention. See, e.g., Meyer et al, Human Molec. Genetics, Vol. 18, pages 546-555, **2009**, at pages 550-1:

> ...We have recently made the striking observation that different mouse U7 gene derivatives that we use for splicing correction are highly expressed in human, but poorly in mouse, cell. **The reasons for this phenomenon are still under investigation**, but this means that a higher expression might be expected in human patients...We are also investigating ways to improve the expression to achieve this goal...

> These findings raise hopes for a therapy for SMA…**However, there is still a long way to go, and it is presently unclear which type of therapy – small drugs, olignucleotides or the type of therapeutic gene used here – will be the first and most successful..**

(internal citations omitted, emphases added).

See also page 546 of this **2009** publication, where the authors admit that Exon 7 of the SMN2 gene is one of the best studied exons of the human genome, yet many hurdles still exist in achieving clinical efficacy: …"the oligonucleotides did not reach the spinal cord, and hence no therapeutic benefit could be demonstrated…"

See also the post-filing publication also provided by Applicant of Marquis et al, Molecular Therapy, Vol. 15, No. 8, pages 1479-1486, **2007**, at page 1483:

> In all four target locations, the addition of the ESE led to a certain let-up in this exclusion effect. This strongly suggests that the enhancer/U7 combination can be used for improving the recognition of many exons in other genes too. **However, our results also demonstrate the necessity of carefully selecting and optimiizing the target locations as well as the ESE sequences.** Only in two instances, i.e., the exonic locations A and B, did the stimulatory effect of the ESE overcome the inhibition caused by the control constructs and lead to a real improvement of exon 7 inclusion. Moreover, targeting of the bifunctional U7 snRNA to position B was more efficient than to position A. The differences in the expression levels of the U7 snRNAs can only partly explain these different stimulatory efficiencies…

(citations omitted, emphasis added).

See also Marquis et al at page 1479, last full paragraph, pointing out the ongoing delivery obstacles that must be overcome in gene therapy: "However, it is unclear whether such oligonucleotides can be delivered to motoneurons, a treatment which would have to be repeated frequently."

The specification fails to teach successful in vitro and in vivo splicing corrections using a representative number of species of the broadly claimed genus, which encompasses a first domain which forms a specific binding pair with any target sequence which is within 100 nucleotides of any defective RNA splicing site on a target RNA, and which nucleic acid molecule further comprises a second specific binding pair with any RNA splicing factor which is optionally a UsnRNP, and which second domain is optionally complementary or non-complementary to any second target RNA species. The specification also fails to teach a representative number of species of nucleic acids providing therapeutic effects for any disease or condition characterized by defective or undesirable RNA splicing in an individual. The examples provided at the time of filing are not representative or correlative of the expansive genus of compounds claimed.

The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of a representative number of compounds claimed, whereby exonic incorporation has been enhanced, and recruitment has occurred for any splicing factor to any target RNA species for treating any condition characterized by defective RNA splicing in an individual. Other experimentation required to practice the invention claimed includes determining accessible target sites, modes of delivery and formulations to target appropriate cells and /or tissues in an organism, whereby the compound or compounds are effectively delivered in adequate quantities to the target cells. Since the specification fails to provide sufficient guidance for the methods using the therapeutic compositions claimed, and since determination of these factors is highly

unpredictable, it would require undue experimentation to practice the invention over the broad scope claimed.

One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus claimed. Thus, Applicant was not in possession of the broadly claimed genus, nor is the full scope enabled.

For these reasons, the instant rejections are maintained.

Rejections Necessitated by Amendments

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 23, 26, 28, 30-38, 40-43, 61- 69, 71-78 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Mitchell et al (US 2003/0077754) and Mitchell et al (US 2004/0126774), and Hofmann et al (Proc Natl. Acad. Sci., Vol 97, No. 17, pages 9618-9623, 2000, provided by Applicant)), and further in view of Lim et al (J. Biol. Chem., Vol. 276, No. 48, pages 45,476-45,483, 2001, see IDS document No. 61, filed 12-30-05), and Lorson et al (Proc. Natl. Acad. Sci., Vol. 96, pages 6307-6311, 1999, see IDS document No. 64, filed 12-30-05), the combination further in view of Dunckley et al (Human Molec. Genetics, Vol. 5, No. 1, pages 1083-1090, 1995, see IDS document No. 32, filed 12-30-05) **insofar** as the claims are drawn to methods of

recruiting RNA splicing factors, enhancing exonic incorporation, and recruiting a splicing factor to a target RNA species **in vitro for testing candidate compounds** for their treatment of a condition characterized by defective RNA splicing in an individual.

Mitchell et al (US 2003/0077754) teach methods of recruiting RNA splicing factors, enhancing exonic incorporation, and recruiting a splicing factor to a target RNA species for treating a condition characterized by defective RNA splicing in an individual, comprising the administration of a nucleic acid molecule comprising a first domain which forms a specific binding pair with a target sequence which is within 100 nucleotides of a defective RNA splicing site on a target RNA, and which nucleic acid molecule further comprises a second specific binding pair with an RNA splicing factor which is optionally a UsnRNP, and which second domain is optionally complementary or non-complementary to the second target RNA species (see the abstract, pages 2-3, figures 1, 2, 3, 6, 8, 9, 20, 21, 23, 24, 37, 40, 41, pages 5-6, 8-9, 14-15; example 8, page 18; example 9, page 19; example 11, pages 22-23; claims 1, 2, 7-11, 16-19, 21-23, 26, 27, 32-36, 42-45, 48, 49).

Mitchell et al (US 2004/0126774) teach methods of recruiting RNA splicing factors, enhancing exonic incorporation, and recruiting a splicing factor to a target RNA species, comprising the administration of a nucleic acid molecule comprising a first domain which forms a specific binding pair with a target sequence which is within 100 nucleotides of a defective RNA splicing site on a target RNA, and which nucleic acid molecule further comprises a second specific binding pair with an RNA splicing factor which is optionally a UsnRNP, and which second domain is optionally complementary or non-

complementary to the second target RNA species, and optionally comprises CAGGUAAGU (see the abstract; pages 1-6, esp. paragraphs 0008----9, 0013, 0015, 0016, 0019-0020, 0037, 0039, 0040, 0042-0044, 0047-0051, 0062, 0065, claims 1-11, 16-36).

Hofmann et al (Proc Natl. Acad. Sci., Vol 97, No. 17, pages 9618-9623, 2000) teach promotion of the inclusion of SMN2 exon 7 in stimulation of full length SMN2 expression in vitro upon transfection of target cells in vitro using commercially available liposomes, and subsequent expression of recombinant Htra2-Beta1, which is an SR-like splicing factor which was found to bind an AG-rich exonic splicing enhancer in SMN exon 7 (see entire document, esp. the text on p. 9618; right hand col. on p. 9619; text on p. 9622).

The primary references do not teach the incorporation of 2'-O-methyl or phosphorothioate internucleotide modifications into oligonucleotides.

Lorson et al (Proc. Natl. Acad. Sci., Vol. 96, pages 6307-6311, 1999, see IDS document No. 64, filed 12-30-05) teach the single nucleotide mutation in the splice site of the SMN gene which regulates splicing and teaches a direct relationship between this single nucleotide mutation, the presence of disease and exon 7 skipping in SMN (see esp. the abstract and introduction on p. 6307, discussion on pages 6310-6311).

Lim et al (J. Biol. Chem., Vol. 276, No. 48, pages 45,476-45,483, 2001, see IDS document No. 61, filed 12-30-05) teach the single nucleotide mutation in the splice site of the SMN gene which leads to the disruption of an exonic splicing enhancer and reduces the strength of the 3'-splice site of exon 7, reduces intron 6 removal, and

increases the efficiency of competing exon 7 skipping pathway, which results in progression of spinal muscular atrophy. Lim also teaches enhanced stability, target binding and cellular uptake of oligonucleotides comprising 2'-O-methyl and phosphorothioate internucleotide modifications (see the abstract, introduction on pages 45,476-45,477; methods on page 45,478; fig. 2 on p. 45,479; discussion on pages 45,480, and 45,482-45,483).

It would have been obvious to design nucleic acid molecules comprising a first domain which forms a specific binding pair with a target sequence of SMN that is within 100 nucleotides of the defective RNA splicing site taught previously by Lorson and Lim, and which nucleic acid molecules further comprise a second specific binding pair with an RNA splicing factor appropriate for recruiting the relevant RNA splicing factors, for reducing exon 7 skipping or optionally for enhancing exonic incorporation, and for recruiting splicing factors to the target SMN RNA for treating spinal muscular atrophy (SMA) because the mutation linking this disease with incorrect or aberrant splicing was well known in the art at the time the instant invention was made. Furthermore, it would have required routine experimentation to design nucleic acid molecules targeting the mutation site previously taught in the art for SMN and relying on the methods taught previously by Hofmann, Mitchell and Mitchell. One of ordinary skill in the art would have had a reasonable expectation of success for correcting the exon skipping phenomenon associated with SMA because the single point mutation causing this exon skipping was well known in the art, and the design of nucleic acid molecules for targeting and correcting this mutation were also well known in the art, relying on the teachings of

Hofmann, Mitchell and Mitchell, whereby administration of recombinant Htra2-Beta 1, or administration of pre-trans-splicing molecules designed to interact with the well known target precursor messenger RNA molecule of SMN would reasonably be expected to lead to trans-splicing to correct the mutated splice site in appropriate target cells in vitro. One of ordinary skill in the art would have been motivated to correct this genetic defect because the relationship between exon skipping and SMA disease severity had been well documented the prior art, and the means of generating pre-trans-splicing molecules to trans-splice the target pre-mRNA were also well known in the art to provide gene therapy approaches for correcting splicing disorders for known mutations.

One of ordinary skill in the art would also have been motivated to incorporate 2'-O-methyl and/or phosphorothioate internucleotide modifications into nucleic acid molecules for target cell delivery and uptake because these modifications were well known in the art to enhance nucleic acid stability from nuclease degradations, as well as enhancing target cell uptake and target binding, as taught previously by many in the field, including Lim et al.

For these reasons, the instant invention would have been obvious to one of ordinary skill at the time the instant invention was made.

Allowable Subject Matter

Seq ID No. 16 (recited in claim 70) appears free of the prior art searched and of record.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. ' 1.6(d)). The official fax telephone number for the Group is 571-273-8300. NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE CO PIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jane Zara whose telephone number is (571) 272-0765.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz, can be reached on (571) 272-0763. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jane Zara
7-17-09

/Jane Zara/

Primary Examiner, Art Unit 1635